Patent Application

**Summary**

A new and unique method for the production of nano/micro sized particles, in the form of solid arbitrary particles and spheres (and hollow spheres, also known as liposomes). The improved and novel ultrasound based method (based on Multifrequency, Multimode, Modulated Sonic & Ultrasonic Vibrations, also known as MMM) enables a resolution of the typically known and current production disadvantages, especially for liposome production, in both laboratory and commercial batch and continuous modes. The improved method enables a much narrower size distribution of resulting particles (typically 5nm to 100nm) along with a much shorter production time (which lies between factor 10 and 100 shorter of typical and known production times) along with a completely non-contamination of the end product.

**Description**

Due to the ever-increasing applications of liposomes in biophysics, physiology and medicine, many techniques have been developed over recent years to manufacture them. Micro and nano sized liposomes can be utilized as carriers of encapsulated drugs. All existing methods for the production of these Liposomes have serious drawbacks, namely rate of production, high production costs, low efficiency, low quality, end product contamination with metal particles during production, short operating life of used ultrasonic processors and difficult scale-up procedures. Specifically, for human drug delivery, liposomes (in the order of micro/nano size) are of growing interest as carriers of drugs. For medical applications, these liposome carriers can be targeted to specific sites within the human body. in various ways to deliver the encapsulated drug through the cell membrane due to the micro/nano liposome size.

Today chemotherapy is still the most common form of medication for the treatment of cancer patients. Through the application of liposomal drug delivery, high overall body dosages (which tend to cause severe side effects) are lowered and significantly higher cancer cell drug concentration can be achieved so as to enhance the therapeutic effects.

Through a new and innovative system of liposome production (high efficiency, selective sizing, batch/continuous methods for commercial production) for the production of the required liposomes, highly effective liposomal drug delivery can be achieved through the coupling with various known targeting methods such as liposome surface coupling with specific proteins.

The application describes a new and unique method for the production of nano/micro sized particles, in the form of solid arbitrary particles and spheres (and hollow spheres, also known as liposomes). The improved and novel ultrasound based method enables a resolution of the typically known and current production disadvantages, especially for liposome production, in both laboratory and commercial batch and continuous modes. The improved method enables a much narrower size distribution of resulting particles (typically 5nm to 100nm) along with a much shorter production time (which lies between factor 10 and 100 shorter of typical and known production times) along with a completely non-contamination of the end product.

Turbulence is created in a mixture of small single particles and/or molecules within a carrier liquid. The turbulence can be created via various methods however, this method utilizes special and unique ultrasonic means. Turbulence, in the form of numerous small vortices within the bulk liquid mixture, are created so enabling the agglomerate and sticking together of individual particles/molecules in a highly concentrated and fast twisting/cyclonic manner.

The turbulence/vortices described above are created through the use of a special submerged bar or rod like resonating element which is activated via a special external electro-acoustic (or ultrasonic) generator. The resonating bar/rod has axial and perpendicular holes and channels, designed in a way that all of them are synchronously resonating, producing different wave motions, vortices and shear waves in both axial and radial directions, when submersed. Subsequently, the uniquely designed resonating bar is able to produce and propagate the required liquid vortices via a combination of low frequency oscillations, ultrasonic frequency oscillations, including forced and frequency-sweeping oscillating regimes with different signal modulations.

**Claims**

1. The creation of micro/nano sized particles through:

the accumulation of numerous smaller particles or molecules

1. The creation of micro/nano sized particles according to claim 1. through the action of turbulence and the sticking together (accumulation) of numerous single smaller particles or molecules which are present in a fluid carrier.
2. The creation of micro/nano sized particles according to claim 2. depending on the specifics of the liquid mixture (of which particles may be biomolecule, ferromagnetic, ions or other particles) various physical methods are employed so as to create a turbulence (such as acoustic, mechanical, optical, electromagnetic or electric field).
3. The creation of micro/nano sized particles according to claim 3. the micro/nano sized particles specifically, for a biomolecule in liquid suspension, an acoustic method is employed for creating the turbulence in the form of numerous small vortices.
4. The creation of micro/nano sized particles according to claim 4. a resonating element is used to create numerous small vortices. Acoustic energy is transferred from an external generator through to a resonating element.
5. The creation of micro/nano sized particles according to claim 5. the resonating element is in the form of a bar or rod structure.
6. The creation of micro/nano sized particles according to claim 5.- 6. a uniquely designed resonating bar is able to produce and propagate the required liquid vortices via a combination of low frequency oscillations, ultrasonic frequency oscillations, including forced and frequency-sweeping oscillating regimes with different signal modulations.
7. The creation of micro/nano sized particles according to claim 5. - 7. the resonating bar has axial and perpendicular holes and channels, designed in a way that all of them are synchronously resonating, producing different wave motions, vortices and shear waves in both axial and radial directions, when submersed in a liquid.
8. The creation of micro/nano sized particles according to claim 5. - 8. the resonating bar produces a very large spectrum of cavitation bubbles of varying diameter unlike traditional ultrasonic methods.
9. The creation of micro/nano sized particles according to claim 5. - 9. the resonating bar is creating progressive ultrasonic waves (defined as directional, pushing waves).
10. The creation of micro/nano sized particles according to claim 4. typically, particles are defined as liposomes.

**Sketches**

1. Example of unique acoustic field produced by resonating element (also known as MMM-Sonorod)
2. Example of unique acoustic field produced by resonating element (also known as MMM-Sonorod)
3. Typical resonating element configuration. (also known as MMM-Sonorod)



**Here we could put numbers and say: 1 (=) MMM ultrasonic transducer, 2 (=) MMM-Sonorod resonator, 3 (=) Waveguide and flange. 4 (=) perpendicular holes**